ELKINGTON AND FIFE LLP

European Patent Attorneys & Chartered Patent Attorneys
Trade Mark Attorneys

JAMES MARCHANT, BSc, CPA, EPA.
GRAHAM BOON, MA, CPA, EPA, RTMA.
DIANA KYLE, BSc, CPA, EPA.
CLIVE FROUD, BSc, CPA, EPA.
PETER CHARLTON, BSc, CPA, EPA, RTMA.
NICK ERTL, M Eng, CPA, EPA.
GORDON WRIGHT, MA, DPhil, CPA, EPA.
SIMON GREENE, MA, PhD, CPA, EPA.
RICHARD GILLARD, BSc, PhD, CPA, EPA.

MARK HIDDLESTON, MA, FITMA, Solicitor

CONSULTANT:
JOHN LEWIN, MA, CPA, EPA.

THAVIES INN HOUSE
3-4 HOLBORN CIRCUS
LONDON EC1N 2HA
TEL:+44 (0)20 7936 8800
FAX:+44 (0)20 7353 4329

PROSPECT HOUSE
8 PEMBROKE ROAD
SEVENOAKS
KENT TN13 1XR
TEL:+44 (0)1732 458881
FAX:+44 (0)1732 450346

E-MAIL: elkfife@elkfife.co.uk
INTERNET: www.elkfife.com

OUR REFERENCE
REG/als/G20711WO

YOUR REFERENCE

PLEASE REPLY TO
LONDON OFFICE

29 October 2004

European Patent Office
(as International Preliminary Examining Authority)
D-80298 Munich
Germany

Dear Sirs

Re: International Patent Application No. PCT/GB2004/001551
PiezOptic Limited

We are writing to file a demand for international preliminary examination and form PCT/IPEA/401 is enclosed herewith. The necessary fees are being paid via our deposit account. We are also filing, as set out hereinbelow, a response to the written opinion of the international searching authority dated 26 July 2004.

We are also taking this opportunity (pursuant to Article 34 PCT) to file amended pages 18-22 to replace the correspondingly numbered pages presently on file which are to be cancelled in their entirety. A copy of the pages presently on file with amendments marked is enclosed for the examiner's assistance. The applicant is not, however, abandoning the deleted-subject matter and reserves the right to file one or more divisional or continuation applications in the national/regional phase.

Claim 1 has been amended to incorporate the features of claim 2. Claims 9 and 10 have been deleted. An additional claim (claim 16) has been added indicating that the pulses of electromagnetic radiation have a frequency of at least 2 Hz. A basis for this amendment may be found in the sentence bridging pages 4 and 5 of the application as filed. Analogous amendments have also been made to the method claims and the claims have been renumbered accordingly.

At parts 1 and 2 of the written opinion under Item V, the examiner is of the preliminary view that the present application lacks novelty and/or inventive step over D1-D4.

D1, D2 and D4 were known to the applicant prior to filing the present application. D1 and D2 are academic papers published by one of the inventors some years prior to the developments disclosed in the present application. D4 is an earlier filed application.

D1 and D2 do refer to time delays between the initial absorption of light and generation of the electrical signal. However, these two documents indicate that this is a negative feature

which should be avoided. Indeed, D2 at the end of part 3.2 indicates that it is important that the signal magnitude be optimised. There is therefore no suggestion that the detector referred to in D1 or D2 would be "adapted" to determine this time delay.

The examiner refers to the use of a lock-in amplifier in D1. However, a possible phase delay between the illumination and the signal is a well-known property of such systems. The delay is dependent on the overall energy transmittance properties of the layer (density, hardness, damping etc.). A lock-in amplifier is used to amplify the signal at a predetermined phase delay, including at zero. There is no statement or implication in D1 that the magnitude of the phase lag should be measured and employed to gather additional information from the film.

Thus reference to "selection of measurement conditions" and particularly "the need to allow for time delays between initial absorption of light and generation of the piezo-electrical signal" simply represents well-established techniques for maximising capture of the energy generated throughout the bulk of the reagent. No attempt is made to generate additional information in the depth of the layer by examining the signal at different time delays as this would examine only a thin cross-section of the reagent and thus will reduce the overall signal, undesirable in a sensor of this form. Crucially, no mention is made of actually determining the time delay at all. Therefore the detector is not adapted to determine the time delay and hence the disclosure of D1 does not anticipate claim 1 of the present application.

D2 is a model study of the factors likely to limit the sensitivity of a gas sensor of the form described in D1. This study provides a great deal of data on the effects of various parameters (flash rate, distance from the film etc.) aimed at helping rationalise the way in which the output from a piezofilm sensor can be optimised (i.e. maximised). Again there is no suggestion that these data could be used to obtain additional information from the sensor and nothing suggesting that information from within the depth of the spot would be of any value in gas sensing. As with D1, the sensor is envisaged as a reagent spot attached to the film from which the total signal is to be maximised. Again, there is no mention of actually determining the time delay between the incident light and the electrical signal. Therefore the detector is not adapted to determine the time delay and hence the disclosure of D2 does not anticipate claim 1 of the present application.

D4 discloses a "phase-locked" amplifier however this merely represents the state of the art in signal processing. A pulsed input locked in phase to a restricted output window is a well-known method of noise reduction, lock-in amplifiers having been around for many years. As explained hereinabove, a lock-in amplifier does not imply that this affords additional information and certainly does not disclose a detector adapted to determine the time delay between the incident light and the electrical signal and hence does not anticipate claim 1 of the present application.

In addition, although page 4, lines 17-19 refers in passing to probing the depth of the interfacial layer, it does not disclose apparatus having a detector adapted to determine the time delay between the incident light and the electrical signal. Indeed, this passage simply implies that if more incident light energy is supplied then more may penetrate into the sample, however there is no mention of the variation in correlation delay, which is vital for depth profiling. Simply varying frequency and amplitude of incident light will not provide any information throughout the depth of the sample.

Regarding inventive step, none of these documents discloses nor makes any suggestion that the concept of correlation delay, i.e. the delay between the incident radiation and the eventual electrical signal, could be used for depth profiling thereby providing information about the position of the species being detected relative to the sensor. The present application is therefore inventive over any of D1, D2 or D4. Combining these documents also brings the skilled person no closer to the present invention.

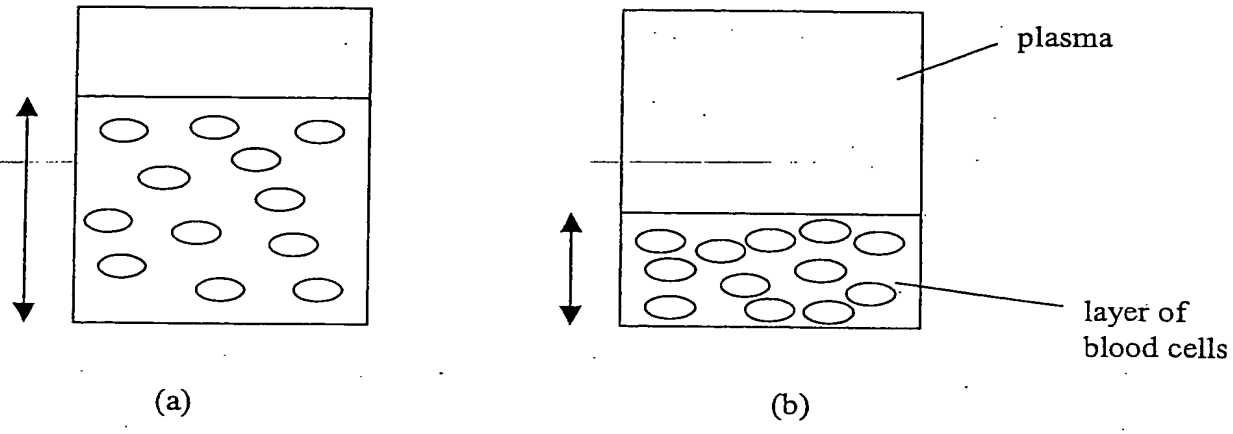
D3 describes a device having a pyroelectric film and two (or possibly more) layers in contact with the film, of which the thermal conductivity, temperature, density and specific heat capacity of each layer are known. Measurements of the intensity and phase difference of the signal can be correlated with changes to one of the physical properties of one of the layers over time. The invention is exemplified by measuring changes in the thickness of layers by the sedimentation of red blood cell sedimentation as well as the movement of an aluminium layer.

D3 does not, however, make any mention of a binding event and hence this document does not disclose a reagent proximal to the transducer which has a binding site capable of binding an analyte. Claim 1 of the present application, as amended, is therefore novel over D3.

With regard to inventive step, D3 and the present invention address quite different technical problems. As outlined above, D3 is concerned with measuring the change in the physical properties of a layer built up in proximity to the pyroelectric film. It achieves this aim by irradiating the layer with low frequency light and measuring the changes in the thermal effects over time.

The device disclosed in D3 may be conceptualised in the following diagrams:

D3



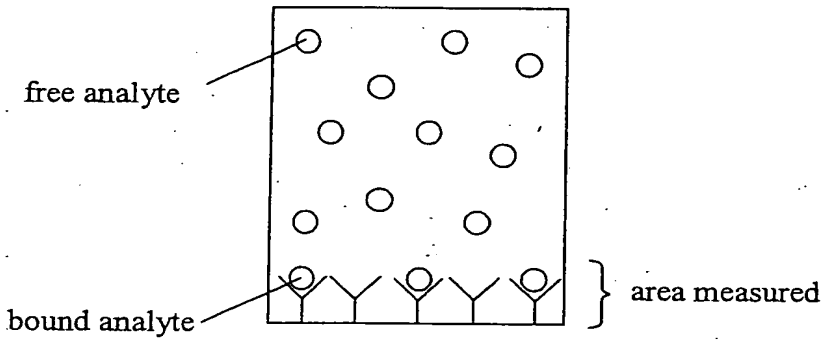
The diagrams show the sedimentation of blood cells over time going from (a) to (b). As time progresses, the thickness of the layer of sedimented blood cells decreases and this change in thickness is measured. It should be noted that all of the blood cells will be detected as one mass, i.e. the layer being detected, and no distinction may be made between different blood cells.

In contrast, the present invention is directed to the differentiation of identical analytes distinguished only be their different positions in a fluid. Indeed, their position relative to

the sensor is critical for application to assays. The present invention achieves this goal by providing a large quantity of energy into the fluid. The energy is absorbed by the adsorbing species providing a thermal shock wave. The correlation delay between the incident energy and the receipt of the signal provides information on the position of the species being detected in relation to the sensor. This information may be used to determine whether or not the species is bound proximally to the sensor or if it is free in solution.

This may be conceptualised in the following diagram:

Invention



As can be seen from the diagram, the bound analyte can be measured by the device of the present application despite the present of the identical but unbound species. The skilled person would find this surprising given the teaching of D3, since D3 indicates that thermal effects from the whole of the sample would be measured. The present applicant has found, however, that this is not the case. By placing a reagent proximal to the surface of the transducer, and applying pulsed electromagnetic radiation, and then measuring the correlation delay, the device of the present invention can distinguish between bound and unbound analytes.

Thus, taking D3 as a starting point, the skilled person seeking to innovate a device for carrying out an assay based on a binding event would not be motivated to ignore the key feature of D3, namely the building up of a layer and then measuring the thermal effects in the whole layer, but instead placing a reagent on the film to bind an analyte and then focusing on the correlation delay to provide information about the position of the analysed species, without the use of inappropriate hindsight from the present application. Indeed, we do not believe that a skilled person looking to improve on existing binding assays would even consider a document such as D3 which relates to the measurement of thermal effects in whole layers. We are therefore of the view that the present invention as claimed is inventive over D3.

With regard to part 4 of the opinion under Item VII, we note the objections and we should be grateful if we could defer addressing these objections until the national/regional phases.

At part 5 of the opinion under Item VIII, the examiner raises a number of objections with regard to lack of clarity. We shall address each of these objections in turn.

At part 5.1 of the opinion, claim has been deleted.

At part 5.2 of the opinion, the amended claims include one independent claim from each category only.

At part 5.3 of the opinion claims 14 and 17 have been amended in order to address this objection.

At parts 5.4 and 5.5 of the opinion, the passages objected to by the examiner have been deleted although where necessary an explanation as to the function of certain components in the device has been included for the sake of clarity. If the examiner maintains his objection, we would propose amending these claims further in the national/regional phases.

At part 5.6 of the opinion the second paragraph at page 2 indicates that energy is generated by non-radiative decay on irradiation with electromagnetic radiation. For ease of reading, we have generally referred to heat and light in the description where appropriate. Page 4, lines 3-8 provides some background on the nature of the energy generated. It is believed that the energy is primarily in the form of heat although other forms of energy, such as a shock wave, may also be generated. In addition, the heat generated may also initiate a pressure wave which is detected by the transducer. We therefore take the view that the term "energy" is actually the clearest term to describe the event. Indeed, we submit that the skilled person would understand that the term "energy" appropriately defines the event which is taking place, namely absorption of the electromagnetic radiation followed by reemission which is detected by the transducer.

We look forward to receiving the IPER in due course, however, if the examiner intends to raise any further objections or maintain the existing objections regarding novelty or inventive step, we should be grateful if the examiner could issue a further written opinion providing us with the opportunity to respond.

Yours faithfully
Elkington and Fife LLP

Richard Gillard

INVESTOR IN PEOPLE

Application No:	GB 0308324.3	**Examiner:**	Geoffrey Pitchman
Claims searched:	1 to 29	**Date of search:**	13 November 2003

Patents Act 1977 : Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance	
A		US 5357111	(OPHIR)
A		US 5048969	(US DEPARTMENT OF ENERGY)

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC[V]:

G1A

Worldwide search of patent documents classified in the following areas of the IPC[7]:

G01K G01N

The following online and other databases have been used in the preparation of this search report:

ONLINE: EPODOC WPI PAJ